1617/11

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: W. Jerry Easterling	§	
SERIAL NO. 10/044,288	§	EXAMINER:
FILED: 10/24/01	§	GROUP ART UNIT: 1619
TITLE: Composition and Method...	§	

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INFORMATION DISCLOSURE STATEMENT

CERTIFICATION UNDER 37 C.F.R. § 1.97(E)

This information is being submitted subsequent to the later of three months after the filing date of the present application or the mailing of the first Office action on the merits, but before the mailing of a final action or the notice of allowance. Accordingly, please charge deposit account No. 50-0894 in the amount of $180.00 to cover the fee under 37 C.F.R. § 1.17(p).

It is respectfully requested that the Examiner indicate consideration of the cited references by returning a copy of the attached form PTO-1449 with initials or other appropriate marks.

If any additional fee is required, or to credit any overpayment, please use deposit account No. 50-0894.

REFERENCES

Please find the following concise explanation of the relevance of the items listed on the attached Information Disclosure Citation Form PTO-1449, copies of patents and other references which are enclosed herewith.

U.S. Patent No. 6,113,939 issued to Place et al. relates to the "treatment of erectile dysfunction by the transurethral administration of an agent" (Column 3, Lines 66-67) directly into the blood

supplying the corpus cavernosum where suitable vaso-dilatory agents include "nitrates such as nitroglycerin and isosorbide dinitrate, long and short acting alpha.-blockers such as phenoxybenzamine, dibenamine, doxazosin, terazosin, phentolamine, tolazoline, prazosin and trimazosin; adenosine, ergot alkaloids, chlorpromazine, haloperidol, yohimbine, verapamil and other calcium blockers, natural and synthetic vasoactive prostaglandins and analogs thereof such as PGE. sub.1, including alprostadil, misoprostol and enprostil, for example, prostaglandin E. sub.2, minoxidil, vasoactive intestinal peptides or any other agent which is capable of producing an erection when administered transurethrally." (Emphasis added; Column 4, Lines 7-18) This sole reference to Verapamil in this patent is to its use as a vasodilator and not in any treatment of a connective tissue disorder.

U.S. Patent No. 5,750,141 issued to Roberts et al. involves how a vaso-active agent, e.g., calcium channel antagonists nifedipine and verapamil, is administered in combination with a therapeutic agent which is useful in the treatment of tissue of the body located below the stratum corneum or the outermost layer of the epidermis. Even though it discussed that "topical" includes administration to the mouth, penis, nose, eye, ear, vagina, anus or any other body part accessible to an aerosol administration of the composition of the invention, there is no discussion of the topical application of calcium antagonists to existing scars -- a seemingly subtle, but highly significant distinction. The only reference to Verapamil in this patent is as an example of a vasodilator compound suitable for topical application and not in any relation to any treatment of a connective tissue disorder. Also, there is no suggestion of a transdermal or topical treatment of Peyronie's disease using Verapamil.

U.S. Patent No. 5,902,609 issued to Lee relates to the prevention of scarring principally through the ***injection*** of calcium antagonists and to the attempted treatment of Dupuytren's contracture

through ***injection*** of same. The mention of topical application to ***wounds*** (i.e. before scarring is in place) is inoperative, because it would prevent proper healing. There is no discussion of the topical application of calcium antagonists to existing scars -- a seemingly subtle, but highly significant distinction.

U.S. Patent No. 5,569,678 issued to Lee relates to the prevention of scarring through the use of calcium channel blockers in the same general manner as the '609 Lee patent, above, which was a CIP of this patent.

U.S. Patent No. 5,773,020 issued to Place et al. on June 30, 1998 mentions Verapamil at Column 4, Line 8, and at Column 4, Lines 43 - 58 mentions, with respect to Peyronie's disease, a "therapeutic agent" may be applied transurethrally, and "may be capable of producing an anti-inflammatory effect on fibrous tissue..." (emphases added), but provides no enabling disclosure of any such method, nor any suggestion of a transdermal treatment of Peyronie's disease using Verapamil.

U.S. Patent No. 5,474,535 issued to Place et al. on December 12, 1995 mentions Verapamil at Column 4, Line 8 and at Column 4, Lines 41 - 55 that, with respect to Peyronie's disease, a "therapeutic agent" may be applied transurethrally, and "may be capable of producing an anti-inflammatory effect on fibrous tissue..." (emphases added), but provides no enabling disclosure of any such method, nor any suggestion of a transdermal treatment of Peyronie's disease using Verapamil.

U.S. Patent No. 5,242,391 issued to Place et al. on September 7, 1993 mentions Verapamil at Column 4, Line 9 and at Column 4, Lines 46 - 61 that, with respect to Peyronie's disease, a "therapeutic agent" may be applied transurethrally, and "may be capable of producing an anti-inflammatory effect on fibrous tissue..." (emphases added), but provides no enabling disclosure of

any such method, nor any suggestion of a transdermal treatment of Peyronie's disease using Verapamil.

U.S. Patent No. 4,338,300 issued to Gelbard discloses throughout the specification the direct injection of collagenase into plaque of Peyronie's disease. At Column 1, Line 44 et seq, Gelbard states "The clinical use of bacterial collagenase has heretofore been limited to topical application for debridement of dermal ulcers and burn eschar." This passage is relevant only to the extent that the present invention, involving the topical, transdermal application of calcium channel blocker(s) is believed to promote the formation of collagenase. There is no suggestion in Gelbard that any substance could be used in topically treating Peyronie's disease and, in fact, teaches away from such a proposition by teaching a much less desirable injection modality.

U.S. Patent No. 5,731,339 issued to Lowrey et al. at Column 2, Lines 24 states "Brindley, G. S. (Br. J. Pharmac. 87:495-500, 1986) showed that, when injected directly into the corpus cavernosum using a hypodermic needle, certain smooth muscle relaxing drugs including "phenoxybenzamine, phentolamine, thymoxamine, imipramine, verapamil, papaverine, and naftidrofuryl" (emphasis added) caused erection. This study noted that injection of an "appropriate dose of phenoxybenzamine or papaverine is followed by an unrelenting erection lasting for hours." Injection of the other drugs studied induced erections lasting from about 11 minutes to about 6.5 hours." At Column 3, Lines 53, et seq, Lowrey teaches the use of Verapamil as a vasodilator. In all known references to Verapamil in this reference, all are to its use as a vasodilator, not in any treatment of a connective tissue disorder. At Column 5, Line 66 et seq, Lowrey includes Peyronie's disease among causes of sexual dysfunction.

U.S. Patent No. 5,139,944 issued to Sawyer et al. mentions at Column 3, Lines 37, et seq the application of leech collagenase directly to plaques of Peyronie's disease in a long listing of

possible uses of the collagenase. However, there is no suggestion of a transdermal treatment of Peyronie's disease using Verapamil.

Patent Specification WO 94/02130 issued to the Massachusetts Institute of Technology mentions in the abstract, page 3, paragraph 3 - page 4, paragraph 2, page 7, paragraph 1, page 8, paragraph 2, page 9, paragraph 2 - paragraph 3, page 11, paragraph 2, and the claims that verapamil is an example of a phenylalkylamine compound effective for "minimizing or preventing excessive scar formation, particularly hypertrophic wound healing disorders, such as hypertrophic scars and keloids" in humans or other mammals. These limited references to Verapamil in this patent are for hypertrophic wound healing disorders and not in any relation to any treatment of any connective tissue disorder.

Patent Specification WO 91/01624 issued to the Massachusetts Institute of Technology mentions on page 3, lines 1-21, page 4, lines 1-9, page 6, line 14 - page 7, line 15, page 8, lines 16-28, and the claims that verapamil, as one example of several listed calcium channel blocking agent, is useful to "minimize hypertrophic wound healing disorders in humans." These limited references to Verapamil in this patent are for hypertrophic wound healing disorders and not in any relation to any treatment of any connective tissue disorder.

Patent Specification WO 94/17839 issued to Arch Development Corporation mentions on page 8, line 19 - page 9, line 13, page 13, line 18 - page 15, line 6, page 15, line 30 - page 16, line 7 that verapamil is an example (out of 7 listed) of a calcium transport blocker (i.e., a calcium antagonist). One aspect of this invention "contemplates a method for improving the appearance and size of scars by covering the scar with a thermal insulating material wherein the material contains a therapeutically effective amount of a [calcium antagonist] medicament." These limited references to Verapamil in this patent are for a method to improve "the size and appearance of a scar

associated with a fibromatosis, a keloid, or a hypertrophic wound healing disorder" by "stimulating collagenase activity in the scar" via "a thermal insulating material that elevates the surface temperature of the scar" and not in any relation to any treatment of any connective tissue disorder.

Patent Specification WO 96/29987 issued to Baker et al. mentions at page 7, lines 6 - 11, page 10, lines 23 - 33, page 12, lines 15 - 17, page 14, lines 9 - 17, page 16, lines 19 - 31, page 17, lines 28 - 33, and claims 1-3 and 17 verapamil. Specifically, "as defined herein, verapamil is an inhibitor of active oxygen." Superoxide dismutase and other active oxygen inhibitors, like verapamil, are "directly applied in combination with a barrier material at local sites of tissue injury to prevent or decrease formation of adhesions and undesirable proliferation of cells." These limited references to Verapamil in this patent are in the context of active oxygen inhibitors and not in any relation to any treatment of any connective tissue disorder.

The only pertinent, non-redundant references known to Applicant include:

Levine et al.; "Intralesional Verapamil Injection for the Treatment of Peyronie's Disease", Journal of Urology; Vol 151, 1522-1524; June 1994 suggests that intralesional calcium antagonist (verapamil) therapy offers an economical and sensible nonoperative approach to the treatment of Peyronie's disease." There is no suggestion in this reference that any substance could be used in topically treating Peyronie's disease and, in fact, teaches away from such a proposition by teaching a much less desirable injection modality.

Levine; "Treatment of Peyronie's Disease with Intralesional Verapamil Injection"; Vol, 158, 1395-1399; October 1997 in which the author discusses the procedure reflected by the title. There is no suggestion in this reference that any substance could be used in topically treating Peyronie's disease and, in fact, teaches away from such a proposition by teaching a much less desirable injection modality.

Rehman et al.; "Use of Intralesional Verapamil to Dissolve Peyronie's Disease Plaque: A Long-Term Single-Blind Study"; Urology; Vol. 51, 620-626 in which the authors discuss the procedure reflected by the title. There is no suggestion in this reference that any substance could be used in topically treating Peyronie's disease and, in fact, teaches away from such a proposition by teaching a much less desirable injection modality.

Willimann et al.; "Lecithin Organogel as Matrix for Transdermal Transport of Drugs"; Journal of Pharmaceutical Science; Vol 81, No. 9; September 1992 in which the authors discuss the use of organogels as transport vehicles of various drugs. Nifedipine (page 872) is mentioned twice, both times in the context of its relative solubility in lecithin gels compared to water or isopropyl palmitate. There is no reference to Verapamil in this article nor any suggestion that any substance could be used in topically treating Peyronie's disease.

Sekine et al.; "Gel Ointment of Verapamil for Percutaneous Absorption"; Drug Design and Delivery; Vol. 1, No. 3; 1987 states that a gel ointment of verapamil (generally pages 245-52) "can be used for transdermal drug delivery when an adequate absorption promoter is added." However, there is no suggestion of a transdermal treatment of Peyronie's disease using Verapamil, nor is there any enabling disclosure of any such method.

Jain et al.; "In Vitro Percutaneous Absorption of Verapamil"; Indian Journal of Experimental Biology; Vol. 34, No. 5; 1996 concludes that verapamil hydrochloride can be administered transdermally (pages 475-7). However, there is no suggestion of a transdermal treatment of Peyronie's disease using Verapamil, nor is there any enabling disclosure of any such method.

Verapamil. The Merck Index (12th Edition), 1996. Entry N 10083. This is an encyclopedic detail of the characteristics of Verapamil, e.g., "coronary vasodilator with calcium blocking activity" that is categorized as an antianginal and a class IV antiarrhythmic. However, there is no suggestion

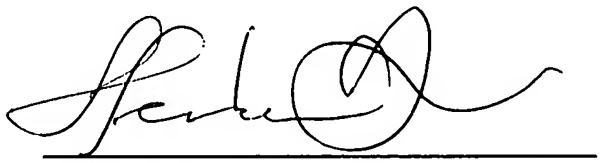
of a transdermal treatment of Peyronie's disease using Verapamil, nor is there any enabling disclosure of any such method.

Riedl et al.; "Iontophoresis for the Treatment of Peyronie's Disease"; Journal of Endourology; Vol. Suppl. 1; 1997 discusses iontophoresis (i.e., the electrokinetic transport) of various compounds, including verapamil, for treatment of Peyronie's disease. However, there is no suggestion of a *transdermal* treatment of Peyronie's disease using Verapamil, nor is there any enabling disclosure of any such method.

The above-listed references are submitted to ensure that the record clearly reflects that the Examiner has considered the references in the examination of Applicant's Application and that s/he makes his/her consideration of them a matter of record.

The Examiner is respectfully requested to consider these references and all previously cited references in the examination of Applicant's application and to make such considerations a matter of record.

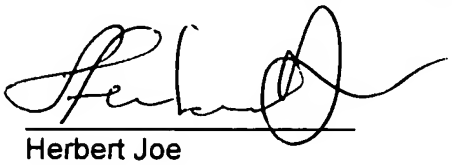
Respectfully submitted,



Herbert Joe
Registration No. 51,338
900 Washington Ave.
5th - 8th Floors
P. O. Box 1470
Waco, TX 76702
(254) 755-4234
(254) 754-6331 (Fax)

CERTIFICATE OF MAILING

I hereby certify that this correspondence and all listed attachments, enclosures and exhibits are being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on this the 8th day of August 2002.



Herbert Joe

Date: 8/08/02